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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,277	11/28/2005	Tadayoshi Mitsuhashi	690107.404USPC	5923

500 7590 11/18/2008

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EXAMINER	
SHAW, AMANDA MARIE	

ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
11/18/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,277	MITSUHASHI, TADAYOSHI	
	Examiner	Art Unit	
	AMANDA SHAW	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 11-19* is/are pending in the application.

4a) Of the above claim(s) *8 and 11-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/29/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Election/Restrictions

1. This action is in response to the amendment filed August 25, 2008. This action is made FINAL.

Claims 1-8 and 11-19 are currently pending. Claims 1-7 have been amended. Claims 8 and 11-19 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected subject matter, there being no allowable generic or linking claims. Claims 1-7 will be addressed herein.

2. Acknowledgment is made that the Applicants have filed an English translation of a certified copy of foreign application Japan 2002-313076, filed 10/28/02.

Withdrawn Rejections

3. The rejections made under 35 USC 102(a) and (b) in sections 6 and 7 of the Office Action of May 23, 2008 are withdrawn in view of amendments made to the claims. Specifically the Applicants amended the claims to recite an active process step of determining if a pig is susceptible or resistant to influenza A.

The rejections made under 35 USC 103(a) in sections 9-11 of the Office Action of May 23, 2008 are withdrawn in view of amendments made to the claims. Specifically the Applicants amended the claims to recite an active process step of determining if a pig is susceptible or resistant to influenza A.

Claim Rejections - 35 USC § 112 2nd paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that the goal of the method and the final step do not agree. The claims are drawn to a method for determining a pig's resistance to influenza A virus. However, the claims recite the final step of determining that a subject pig is susceptible to influenza A virus when the 11 base deletion is detected or the subject pig is resistant to the influenza A virus when the deletion is not detected. While the steps listed in the method result in the determination if a pig is resistant to influenza A and relate back to the preamble of determining a pig's resistance to an influenza virus, they also result in the determination if a pig is susceptible to influenza A which does not relate back to the preamble. Therefore, it is unclear as to whether the claims are intended to be limited to a method for determining a pigs resistance to an Influenza A virus or a method of determining a pigs susceptibility to an influenza A virus or a method where both is determined.

Claims 1-7 recites the limitation "the deletion is not detected". There is insufficient antecedent basis for this limitation in the claim because although the claims previously refer to an “11 base deletion” they do not refer to a “deletion”. Therefore it is unclear if “the deletion that is not detected” is the 11 base deletion of some other deletion.

Claim Rejections - 35 USC § 112 1st paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for determining a pig’s susceptibility to influenza A, wherein the method comprises: obtaining a sample of nucleic acid from a pig, directly assaying said sample for an 11 bp deletion in a swine Mx1 gene, wherein the deletion is from positions 2064 to 2074 in the nucleotide sequence of SEQ ID NO: 1, and determining that said pig has a high susceptibility to influenza A when the 11 bp deletion is detected in comparison to other pigs that do not have the 11 bp deletion, does not reasonably provide enablement for a method for determining a pig’s resistance to influenza A. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The invention is drawn to a method for determining a pig's resistance to influenza A virus. The claims comprise detecting an 11 bp deletion in a swine Mx1 gene exon, wherein the deletion is from positions 2064-2074 in the nucleotide sequence of SEQ ID NO: 1. The nature of the invention requires the knowledge of a reliable association between the presence and/or absence of the 11 bp deletion and a pig's resistance to influenza A virus. In the instant case the term "resistance" is broad because it encompasses any level of resistance such as complete resistance or partial resistance.

The specification (page 3) teaches that in a previous study the inventors revealed that among domesticated pigs, some have an 11 bp deletion in the gene encoding the Mx1 protein, which is responsible for the suppression of myxovirus propagation. They further teach that the 11 bp deletion in the last exon of the Mx1 gene causes a frame shift of codons which relocates the stop codon to a much further position downstream and thus dramatically alters the downstream amino acid sequence. The resultant Mx1 protein has a different molecular weight and structure compared to the normal (wild type) protein, and has probably lost is ability to suppress virus propagation because of that.

The specification teaches (page 3) that the present inventors introduced a normal (wild type) Mx1 gene, a mutant Mx1 gene containing a 3 bp deletion in exon 13, a mutant Mx1 gene containing the 11 bp deletion in the last exon, or an empty vector into murine 3T3 cells which have no Mx1 activity and performed influenza A virus infection experiments. As shown in Fig 3 the 3 bp deletant had a virus propagation curve comparable to that of the wild type and the deletion did not affect the virus suppression

ability. However the 11 bp deletant completely lost its ability to suppress virus propagation and had a virus propagation comparable to that of the empty vector. It is further noted that while the 3 bp deletant and the wild type were able to suppress the virus longer than the empty vector and 11 bp deletant, all of the these eventually were infected suggesting that the absence of the 11 bp deletant does not mean that the sample will be "resistant" to the virus it just means that it can suppress it longer.

Based on the teachings in the specification it is unpredictable what can be concluded based on the Applicants experiments. While the Applicants have shown that the 3 bp deletant and the wild type were able to suppress the virus longer than the empty vector and 11 bp deletant, all of the these eventually were infected suggesting that the absence of the 11 bp deletant does not mean that the sample will be resistant to the virus it just means that it can suppress it longer. Thus the absence of the 11 bp deletant does not appear to make the sample "resistant" to the virus it only appears to suppress the virus for a longer amount of time, yet the claims are drawn to a method for determining a pig's resistance to an RNA virus.

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the

art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the claims do not bear a reasonable correlation to the scope of enablement because the specification only teaches that pigs that carry the 11 bp deletion have a high susceptibility to influenza A in comparison to other pigs that do not have the 11 bp deletion. Based on the data in Figure 3 absence of the 11 bp deletant does not appear to make the sample “resistant” to the virus it only appears to suppress the virus for a longer amount of time. Accordingly, the specification does not teach those skilled in the art how to make and use the full scope of the claimed invention.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morozumi (Biochemical Genetics 8/2001) as evidenced by Muller (Experientia 1991).

Regarding claim 1, Morozumi teaches that they carried out PCR-RFLP on genomic DNA of 341 pigs from 15 different breeds. They found three different

polymorphisms, one of which was an 11 bp deletion from positions 2064-2074 of the porcine Mx1 gene (pages 254 and 256 also Fig 1). Thus Morozumi teaches detecting an 11 bp deletion in a swine Mx1 gene exon, wherein the deletion is from positions 2064 to 2074 in the nucleotide sequence of SEQ ID NO: 1.

Regarding Claim 2, Morozumi teaches that genomic DNA was obtained from the pigs. Exon 14 was amplified using a forward and reverse primer and the amplified PCR fragments were sequenced on an ABI 3700 sequence (pages 253-254). Thus Morozumi teaches preparing a DNA sample from subject pig, amplifying the region of the Mx1 gene that comprises the 11 bp deletion, since Morozumi teaches amplifying all of exon 14, and determining the nucleotide sequence of the amplified DNA.

Regarding Claim 3, Morozumi teaches that genomic DNA was obtained from the pigs. Exon 14 was amplified using a forward and reverse primer and the amplified PCR fragments were digested with the restriction endonucleases NarI and NaeI. The digest PCR product were electrophoresed through 1.5% agarose gel, thereby separating the DNA fragments based on their size. Morozumi further teaches that the gel was photographed and shows a comparison of the sizes of detected DNA fragments (See Figs 2 and 3).

Regarding Claim 4, Morozumi teaches that genomic DNA was obtained from the pigs. Exon 14 was amplified using a forward and reverse primer and the amplified PCR fragments were digested with the restriction endonucleases NarI and NaeI. The digest PCR product were electrophoresed through 1.5% agarose gel, thereby separating the DNA fragments based on their size. Morozumi further teaches that the gel was

photographed and shows a comparison of the sizes of detected DNA fragments (See Figs 2 and 3).

Regarding Claims 1-4 Morozumi does not teach a method further comprising determining that a subject pig is susceptible to influenza A when the 11 bp deletion is detected or that the subject pig is resistant to the influenza A virus when the 11 bp deletion is not detected.

However Morozumi discloses that in the mouse, loss of resistibility to influenza virus has been shown to be due to specific polymorphisms in the Mx gene (abstract). Specifically deletions and frame shifts in the murine Mx1 gene have been shown to be related to influenza virus susceptibility (page 259). Morozumi states that particularly the carboxyl terminal region of Mx1 has been reported to be involved in the antiviral function in the mouse and human (page 253). Here it important to note that the claimed 11 bp deletion results in a frame shift with many amino acid substitutions and extension of the carboxyl terminal region of the Mx1 protein. This extension of the carboxyl terminus of the protein might cause a significant change in the conformation and function of porcine Mx1 protein (page 257). Morozumi further states that it will be interesting to determine if the 11 bp deletion is associated with variation in resistance to the myxovirus family in the pig (abstract).

As evidenced by Muller it was well known in the art at the time of the invention that genetic analysis had established that in mice the antiviral state directed against influenza A and B viruses is controlled by the autosomal dominant $Mx1^{+}$ allele. Muller teaches the mice strains with the $Mx1^{-}$ alleles are sensitive to influenza virus infections.

The $Mx1^-$ genotype is characterized with by large deletions or a nonsense mutation within the $Mx1^-$ gene that abolishes synthesis of functional Mx1 protein (page 927).

Accordingly, based on the disclosure of Morozumi it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Morozumi by further determining if the 11 bp deletion is associated with variation in resistance to influenza A in pigs. The prior art of Morozumi as evidenced by Muller teaches that deletions and frame shift mutations in the carboxyl terminal region of murine Mx1 are associated with resistance to influenza A. Since the claimed 11 bp deletion also occurs in the carboxyl terminal region of the Mx1 gene it would have been obvious to determine if this mutation is also associated with variation in resistance to influenza A in pigs because a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. Further one would motivated to determine if the 11 bp deletion is associated with variation in resistance to influenza A in pigs because Morozumi teaches that influenza is widespread in pigs and the virus causes transient illness and some mortality. Morozumi further teaches that pigs are also involved in the transfer of influenza virus from migratory birds to humans by means of gene conversions of the virus in pigs. Therefore the pig plays an important role in influenza virus propagation in animals and humans.

8. Claims 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morozumi (Biochemical Genetics 8/2001) as evidenced by Muller (Experientia 1991) in view of Singh (US Patent 6322980 2001).

The teachings of Morozumi as evidenced by Muller are presented above.

Regarding Claim 5 Morozumi does not teach a method comprising preparing a DNA sample form a pig, amplifying the region that comprises positions 2064-2074 of SEQ ID NO: 1, dissociating the amplified DNA into single strands, separating the single stranded DNAs on a non denaturing gel and comparing the gel mobility of the fractionated single stranded DNAs. Regarding Claim 6 Morozumi does not teach a method of preparing a DNA sample from a pig, amplifying the region that comprises positions 2064-2074 of SEQ ID NO: 1, determining the molecular weight of the DNA amplified using mass spectrometry and comparing the molecular weight. Regarding Claim 7 Morozumi does not teach a method of preparing a DNA sample from a pig, amplifying the region that comprises positions 2064-2074 of SEQ ID NO: 1, preparing a substrate with an immobilizes probe, contacting the DNA with the substrate, determining the intensity of hybridization.

However Singh discloses multiple methods for detecting the presence of nucleic acid variants. For example Singh discloses SSCP which comprises all of the steps required by claim 5, sizing by mass spectroscopy which comprises all of the steps required by claim 6, and high density array hybridization which comprises all of the steps required by claim 7.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention to substitute the deletion detection method of Morozumi for any of the deletion detection methods of Singh because the substitution of one method would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Response To Arguments

9. Regarding the rejection made under 35 USC 112 2nd paragraph, the Applicants state that they have amended the claims so that the goal of the claimed method agrees with the recited steps. This amendment has been reviewed however the claims are still problematic because it is unclear as to whether the claims are intended to be limited to (i) a method for determining a pigs resistance to an Influenza A virus or (ii) a method of determining a pigs susceptibility to an influenza A virus or (iii) a method where both are determined. For further explanation please see paragraph 4 above.

Regarding the rejection made under 35 USC 112 1st (enablement) the Applicants submit that the terms "resistance" and "resistant" are used within there ordinary and customary meaning. Additionally the Applicants traversed the Examiners conclusion that the absence of the 11 bp deletion does not appear to make the sample resistant to the virus, but rather, the deletion only appears to suppress the virus for a longer amount of time. The Applicants cite the specification (page 19, lines 25-26) for support. Here the specification states that no further increase in the viral propagation was recorded in the wild type Mx1 expressing 3T3 cells after 48 hours, thus, indicating viral propagation was suppressed (see Fig 3).

This argument has been fully considered but is not persuasive because the terms “resistance” and “resistant” have not been defined in the specification. Therefore the claims have been interpreted broadly to mean that when the 11 bp detection is not detected the pig has “complete” resistance to influenza A. Figure 3 in the specification clearly shows that this is not that case. Specifically Figure 3 shows that the wild type cells were able to suppress the virus for the first 24 hours after infection, however by hour 30 the virus titer was ~2 and by hour 48 the virus titer was ~3. Therefore this is evidence that the wild type cells were not “completely” resistant to the infection, they just were able to suppress the infection for a longer amount of time in comparison to the cells with the 11 bp deletion. Further it is noted that the applicants have not provided any evidence that the terms "resistance” and “resistant” are actually being used within there ordinary and customary meaning in the specification. As set forth in MPEP 716, The arguments of counsel cannot take the place of evidence in the record. Thus the enablement rejection is maintained.

Several of the arguments based on the art rejection are considered moot in view of the amended claims. However the arguments based on the 103(a) rejection made over Morozumi in view of Singh are still relevant. The Applicants argue that Singh teaches methods for detecting SNPs and is completely silent with regard to detecting deletions. Further they argue that the examiner has violated one of the basic tenets in patent law in applying 103 in that the references must be view without the benefit of hindsight afforded by the claimed invention.

This argument has been fully considered but is not persuasive because even though Singh was concerned with detecting SNPs the passages relied upon in the Singh reference were taken from a section of the patent that describes general methods that were known in the art for detecting all different types of mutations. These methods are not used only for detecting SNPs as argued by the Applicants. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
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/Carla Myers/
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